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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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APR 2 1 1993

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Metribuzin: Review of Toxicology Data Submitted under FIFRA section 6(a)(2) by the Registrant.

Caswell No: 33D
Submission: S436338
MRID No: 426725-01
DP Barcode: D188802

FROM: Timothy F. McMahon, Ph.D., Toxicologist 4/13/93
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

TO: Eric Feris / PM 71
Registration Division (H7505C)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head Y. M. Ioannou 4/13/93
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief 4/19/93
Toxicology Branch II
Health Effects Division (H7509C)

Registrant: Miles, Inc.

Action Requested: Review of a chronic toxicity / carcinogenicity study in rats with Metribuzin technical.

184-2

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Conclusions:

The registrant submitted a study entitled, " Technical Grade Metribuzin (Sencor ®): A Combined Chronic Toxicity / Oncogenicity Feeding Toxicity Study in the Rat." This study was submitted under FIFRA section 6(a)(2), based upon the finding by the registrant of a systemic NOEL less than 100 times the existing ADI. The summary and conclusions from review of this study are presented below.

Technical metribuzin was administered to male and female rats in the diet for either 52 or 104 weeks at doses of 0, 30, 300, and 900 ppm (0, 1.3, 13.8, and 42.2 mg/kg/day in males; 0, 1.6, 17.7, and 53.6 mg/kg/day in females). In males and females, systemic toxicity in the form of reduced body weight gain, ophthalmologic abnormalities, changes in absolute and relative organ weights, and increases in the incidence of non-neoplastic pathology were evident at the 900 ppm dose level, establishing this as a maximum tolerated dose for the study. Statistically significant increases in blood levels of thyroxine (T4) and statistically significant decreases in blood levels of triiodothyronine (T3) were observed at all dose levels in male and female rats dosed for either one or two years with technical metribuzin beginning at 91 days, and continuing until study termination in the 2 year group. Thyroid / body weight ratio was significantly increased at all dose levels of metribuzin in male rats assigned to the one year portion of the study. The thyroid was considered a target organ of metribuzin in this study. based on increases in thyroid weight in male and female rats at all dose levels and histological changes in the thyroid of male rats at the 300 and 900 ppm dose levels.

There was no evidence for a carcinogenic effect of metribuzin in this study.

The No Observed Effect Level (NOEL) < 30 ppm

The Lowest Observed Effect Level (LEL) = 30 ppm (males and females; increased absolute and relative weight of the thyroid; decreased lung weight; significant changes in T4 and T3 levels).

The Maximum Tolerated Dose (MTD) = 900 ppm (males and females; decreased body weight and body weight gain).

Results of this study will be presented before the Health Effects Division RfD Committee for reconsideration of the RfD value for metribuzin.

12.

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Classification: core minimum - carcinogenicity ; **core supplementary** - chronic toxicity

This study satisfies the guideline requirements for a carcinogenicity study in rats, but does not satisfy the requirements for a chronic toxicity study in rats, due to the lack of establishment of a systemic NOEL.

Reviewed by: Timothy F. McMahon, Ph.D. 4/12/93
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 4/12/93
Section I, Toxicology Branch II (H7509C)

Data Evaluation Report

Study type: Combined Carcinogenicity/Chronic Toxicity - rats
Guideline: 83-5

EPA ID Numbers: MRID number: 426725-01
ToxChem No: 101101
Submission: S436338
DP Barcode: D188802

Test material: Metribuzin

Synonyms: 4-Amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one; SENCOR

Study number(s): 88-271-BM

Sponsor: Bayer AG
Germany

Testing Facility: Miles, Inc.
Agriculture Division; Toxicology
Stilwell, KS 66085-9104

Title of report: Technical Grade Metribuzin (Sencor ®): A Combined Chronic Toxicity / Oncogenicity Feeding Toxicity Study in the Rat.

Author(s): M.R. Christenson; B.S. Wahle

Study Completed: January 15, 1993

Conclusions:
Technical metribuzin was administered to male and female rats in the diet for either 52 or 104 weeks at doses of 0, 30, 300, and 900 ppm (0, 1.3, 13.8, and 42.2 mg/kg/day in males; 0, 1.6, 17.7, and 53.6 mg/kg/day in females). In males and females, systemic toxicity in the form of reduced body weight gain, ophthalmologic abnormalities, changes in absolute and relative organ weights, and increases in the incidence of non-neoplastic pathology were evident at the 900 ppm dose level, establishing this as a maximum tolerated dose for the study. Statistically significant increases in blood levels of thyroxine (T4) and statistically significant decreases in blood levels of

triiodothyronine (T3) were observed at all dose levels in male and female rats dosed for either one or two years with technical metribuzin beginning at 91 days, and continuing until study termination in the 2 year group. Thyroid / body weight ratio was significantly increased at all dose levels of metribuzin in male rats assigned to the one year portion of the study. There was no evidence of a tumorigenic response to metribuzin in this study.

The data in this study support the conclusion of no evidence of carcinogenicity for technical metribuzin.

The No Observed Effect Level (NOEL) < 30 ppm

The Lowest Observed Effect Level (LEL) = 30 ppm (males and females; increased absolute and relative weight of the thyroid; decreased lung weight; significant changes in T4 and T3 levels).

The Maximum Tolerated Dose (MTD) = 900 ppm (males and females; decreased body weight and body weight gain).

Classification:

chronic toxicity - supplementary
carcinogenicity - minimum

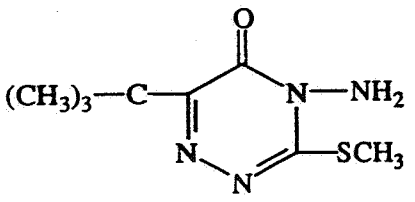
This study satisfies the guideline requirements (§83-5) for a carcinogenicity study in rats, but does not satisfy the guideline requirements for a chronic toxicity study in rats, due to the lack of establishment of a systemic NOEL.

I. MATERIALS AND METHODS

A. Test Material

Metribuzin - description: white powder
purity: ~ 93.0%
reference # 77-297-50

structure:



B. Test Animals

A total of 318 male and 300 female (nulliparous and non-pregnant) Fischer [CDF(F-344)/BR] rats were obtained from Charles River Laboratories, Raleigh, N.C. At arrival, rats were approximately 4-5 weeks old. Weight (week 0): toxicity group - males, 137-179g (mean: 160.0±8.2g); females, 103-126g (mean: 115.2±3.8g) carcinogenicity group (week 0) - males, 122-187g (mean: 156.0±5.9g); females, 65-130g (mean: 112.6±2.9g)
Note: In the 300 ppm dose group for females, one rat (# 2139) was found to have an initial body weight of 65.2g). This rat was replaced at the beginning of the stud

C. Animal Husbandry

Upon arrival (January 24, 1989), rats were examined and any animal showing deviations in general appearance and/or behavior was sacrificed. Rats considered acceptable were housed individually in stainless steel wire mesh cages. Health status of the rats was assessed daily during the 7 day acclimation period prior to commencement of dosing. All rats received Purina Mills Rodent Lab Chow # 5001-4 and tap water *ad libitum* during the study. Environmental conditions were stated as: light cycle (12 hour light/dark); temperature (18 - 25 ^{o}C) and humidity (40 - 70%). Clean cage racks were provided for changing at least once every 3 weeks.

D. Dietary Mixture Preparation

Metribuzin was dissolved in ethanol and then mixed with feed which had been coated with corn oil to facilitate homogeneous distribution within the feed. Control diet was prepared in a like manner, excluding only test substance. All feed mixtures were prepared weekly and stored in a freezer until use.

E. Stability and Homogeneity

For homogeneity analysis, metribuzin was mixed with rat diet to produce concentrations of 20 and 1500 ppm. After mixing in a Hobart mixer, the mixture in the bowl was sampled in triplicate from the top, middle, and bottom of the bowl.

For stability analysis, metribuzin mixed with rodent diet at 20 and 1500 ppm was sampled immediately after mixing. The remaining mixture was divided into 2 portions which were stored in the freezer for 7 days. After 7 days, one portion was removed and stored at room temperature for 0, 1, 3, 7, and 10 days, while the other portion was analyzed. The portion stored at room temperature was also analyzed at the indicated times.

Results of analysis for achieved concentration of test article in test diets (page 4526 of the report) showed that at 30 ppm, the mean achieved concentration of metribuzin was 87.3% of nominal for the study duration, while at 300 and 900 ppm, achieved concentration was 96% of nominal.

Analysis for homogeneity of dietary test mixtures (page 4524 of the report) showed that test material was homogeneously distributed within the diet (means of 18.9 ppm for the 20 ppm level - 94% of nominal, and 1391 ppm for the 1500 ppm level - 93% of nominal).

Stability analysis (page 4525 of the report) showed that at 20 ppm, storage at room temperature had no significant effect on concentration of test material. Storage at room temperature for the 1500 ppm concentration showed that over a 10 day period, concentration of metribuzin appeared to decline from 100% of nominal to 90.8% of nominal. However, concentration of metribuzin at 14 days appeared to rebound to 100% of nominal with no explanation from the registrant, other than that it was considered acceptable if greater than 80% of test material is recoverable after 7 days' storage. Under conditions of freezing, no loss of test material greater than 6% was observed at either 20 or 1500 ppm metribuzin.

F. Experimental Design and Dosing

Following acclimation, rats were randomly assigned to dose groups based upon computerized weight stratification. Based on time constraints, dose groups were not started on test diets on the same day. Instead, start of dosing was staggered, such that control, low, mid, and high dose groups received test article on Monday, Tuesday, Wednesday, and Thursday of the week. Rats were assigned to 3 basic groupings:

1) This group consisted of 20 males and females in the control and high dose groups, and 10 males and females in the low and mid dose groups. These rats received test article in the diet for 55 weeks for assessment of chronic toxicity.

2) In this group, 50 rats/sex/dose were administered test article in the diet for approximately 106 weeks. This group represented the carcinogenicity dose group

3) In the third group, 8 rats/dose/sex received test article in the diet at the same dose levels as the other 2 groups for 28 days. This was done as a precautionary measure in case any rats in the other 2 groups died unexpectedly or developed severe problems. From this group, 3 rats were used as replacements for rats in the main study. The remaining rats in this groups were sacrificed after 28 days.

G. Dose Selection

According to the study report (page 20), doses for the present study were chosen based upon previous subchronic and chronic work showing that an MTD and NOEL would be expected between 750-1500 ppm and 25-60 ppm, respectively. In addition, dosages for the present study were discussed with and acknowledged by Drs. Quang Bui and Stephen Dapson, HED, in a meeting held on December 7, 1988.

H. Statistical Analysis

Survival differences were estimated by the product-limit procedure of Kaplan and Meier. Survival curves were compared using the log-rank and Wilcoxon tests. Continuous data were first analyzed for homogeneity using Bartlett's test. Group means were further analyzed by one-way ANOVA followed by Dunett's test. Data based on unequal variances were compared using Kruskal-Wallis followed by Mann-Whitney U-test. Nontumor frequency data were examined for trends, and data suggestive of a potential effect were then compared using Chi-square and Fisher's exact test. Tumor data were analyzed using a Peto analysis for any primary neoplasm that occurred more than once in any test group. Statistical significance was set at $p < 0.05$. All analyses were performed using software from either INSTEM Computer Systems, Ajit K. Thakur, SAS Institute, or Graham Laboratories.

I. Compliance

A signed statement of data confidentiality claims was provided. Information claimed as confidential was removed to a confidential attachment, and is cited by cross reference within the study.

A signed statement of GLP compliance was provided.

A signed statement of quality assurance was provided.

A signed statement of flagging studies for potential adverse effects was provided. This study meets or exceeds criterion * of 40 CFR 158.34.

II. OBSERVATIONS AND RESULTS

A. Mortality

Individual body weight was recorded weekly for all rats, and again prior to necropsy to obtain organ to body weight ratios. General clinical observations were scheduled for twice a day and once on weekends, while detailed physical examinations were performed once each week. Clinical examinations included palpation for detectable masses. Rats were observed early each morning and again in the afternoon for signs of mortality and/or moribundity. On weekends, the second observation time was made at midday. Any animal showing signs of debility or intoxication was killed by CO_2 asphyxiation and subjected to detailed macroscopic examination. Tissues were preserved in 10% buffered formalin where possible.

Cumulative mortality in male and female rats assigned to the carcinogenicity portion of the study is summarized in the following Table (Table 1):

TABLE 1

Cumulative Mortality in Rats Given Metribuzin in the Diet for 104 Weeks [a]

Week of Study	Males				Females			
	0	30	300	900	0	30	300	900
1	0(0)[b]	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
13	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
26	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
52	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
78	1(2)	3(6)	1(2)	0(0)	3(6)	3(6)	2(4)	3(6)
104	18(36)	21(42)	17(36)	19(38)	12(24)	16(32)	13(26)	10(20)

[a] data taken from page 267 of the report.

[b] cumulative mortality (percent mortality)

At 104 weeks, no significant differences in mortality were observed between control and treated rats of either sex over the duration of treatment. It is noted that sacrifice of rats began at week 105, and lasted until week 107.

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B. **Body Weights**

Group mean body weights at selected times are presented in **Table 2.**

TABLE 2
Group Mean Body Weights in Male and Female Rats Given Metribuzin in the Diet for 104 Weeks [a]

Week of Study	Males (g)				Females (g)			
	0	30	300	900	0	30	300	900
0	148	154*	159*	162*	109	112	112	116*
1	181	186	188*	189*	122	123	123	124
13	317	321	317	302*	177	177	172*	164*
26	359	371*	362	348	198	195	191*	179*
52	407	414	408	393*	220	216	208*	198*
104	347	349	342	324*	269	258	253*	234*

[a]data taken from Table BW-MEAN, pages 74-127 of the report.

At week 13 of the study, absolute body weight was significantly decreased in male rats at the 900 ppm dose level in comparison to controls, and was significantly decreased in female rats at the 300 and 900 ppm dose levels compared to control. Although statistically significant, these decreases were only between 3-7% from control. This could be partly attributed to increased weight of treated rats at the start of the study, due to staggering of rats put on test.

At weeks 26, 52, and 104, statistically significant decreases in absolute body weight were observed in female rats at the 300 and 900 ppm dose levels, while significant decreases in body weight were observed in male rats at weeks 52 and 104. The decreases in female rats at these time points appeared slightly larger (~ 10%) than in male rats (3-6%).

Effects of test article treatment on body weight gain in male and female rats are summarized in the following Table (**Table 3**):

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TABLE 3
Group Mean Body Weight Gains in Male and Female Rats Given Metribuzin in the Diet for 104 Weeks [a]

	Males				Females			
	0	30	300	900	0	30	300	900
Body weight (week 0)	148	154*	159*	162*	109	112	112	116*
Weight gain (grams):								
0-13	169	167	158	140	68	65	60	48
%control	-	99	93	83	-	95	88	70
0-52	259	260	249	231	111	104	96	82
%control	-	100	96	89	-	94	86	74
0-104	199	195	183	162	160	146	141	118
%control	-	98	92	81	-	91	88	74

[a] data calculated from Table 2 of this review.

In male and female rats, dose-related effects on body weight gain were evident in all treated groups. At 13 weeks, decreases of 7% and 17% were observed in male rats at the 300 and 900 ppm dose levels, while in female rats, decreases of 12% and 30% were observed at these same dose levels. For the study duration, body weight gain in male rats was reduced by 8% and 19% at 300 and 900 ppm, while weight gain in female rats was reduced 12% and 26% at these same dose levels. No significant effects on body weight gain were observed at 30 ppm in either sex.

C. **Food Consumption and Efficiency**

Food consumption was calculated for each rat on a weekly basis. by measurement of the amount of food given and that remaining in the hoppers. Scattered food was estimated twice each week and included in the food residue for calculation of the food consumption. Food efficiency was not calculated by the registrant in this study.

Group mean food consumption data are presented in **Table 4** below:

TABLE 4

Group Mean Food Consumption in Male and Female Rats Given Metribuzin in the Diet for 104 Weeks [a]

Food consumption (g/rat/day)

Weeks	Males				Females			
of Study	0	30	300	900	0	30	300	900
1	15.98	15.95	16.12	15.32*	11.31	11.55	11.17	10.34*
%control	-	100	100	96	-	102	98	91
13	17.11	17.29	16.78	16.54	11.87	11.78	11.39*	10.99*
%control	-	101	98	97	-	99	95	92
52	17.69	17.36	17.62	17.42	12.66	12.43	11.61*	11.68*
% control	-	98	99	98	-	98	91	92
78	17.78	17.64	17.75	16.88*	13.64	13.92	13.26	13.29
%control	-	99	99	95	-	102	97	97
104	15.47	14.96	15.43	14.81	13.24	12.11*	12.89	12.27*
%control	-	96	99	96	-	91	97	93

[a] data taken from from Table FC-MEAN, pages 157-210 of the report.

* significantly different vs control ($p < 0.05$)

Food consumption as shown above was significantly decreased in male rats at the 900 ppm dose level on week 78, although from a biological standpoint, this decrease was only approximately 5% in relation to control, and thus does not appear toxicologically relevant. In female rats, significant decreases in food consumption are shown for weeks 13 and 52 at the 300 and 900 ppm dose levels, but again, it is stressed that these decreases were minor (4%) and do not appear toxicologically relevant. It is noted that female rats consumed less food on a g/rat/day basis than male rats in this study.

From the above summary data on body weight and food consumption, it is possible to support an effect of test article at the 900 ppm dose level in male rats, and at the 300 and 900 ppm dose levels for female rats. This is based upon a decrease in body weight gain of greater than 10% for males at the 900 ppm dose level, and a similar effect in females at the 300 and 900 ppm dose levels, while no toxicologically relevant change in food consumption was recorded for male and female rats.

D. Intake of Metribuzin

The group mean intake of metribuzin for male and female rats over the course of the study is summarized in the following table (**Table 5**):

TABLE 5

Group Mean Achieved Dosage of Metribuzin in Male and Female Rats Over 104 Weeks[a]

Dose Group (ppm)	Nominal mg/kg/day (ppm/20)	Average Intake (weeks 1-104) (mg/kg/day)	
		males	females
0	0	0	0
30	1.5	1.3	1.6
300	15	13.8	17.7
900	45	42.2	53.6

[a]data taken from Table AI-MEAN, page 212 of registrant report.

Achieved dosage of metribuzin was calculated from feed consumption, body weight, and diet analysis data. Average intake for the 104 week dosing period in rats assigned to the carcinogenicity portion of the study was 86-92% of nominal values for male rats across all dose levels, and 106-119% of nominal for female rats across all dose levels. Based on a comparison of average dose levels received by male and female rats, it can be concluded that female rats received between 23-28% more test chemical at each dose level than male rats. Although female rats consumed less food on a g/rat/day basis, intake of food was apparently greater on a g/kg body weight/day basis in comparison to males.

E. Ophthalmoscopic Examination

Following acclimation to the laboratory environment but prior to administration of test diets, ophthalmic examinations were performed on all animals. In addition, exams were conducted on all surviving members of the 1 and 2-year treatment groups just prior to sacrifice.

Results of ophthalmic examinations were reported in Appendix IX, pages 4533-4536 of the report. In the one year toxicity group, no ocular abnormalities related to treatment were observed. Although the incidence of chromodacryorrhea was elevated in males of the 900 ppm dose group (incidences of 2/20,2/10,4/10, and 9/20), this was stated as not statistically significant when compared to control, and was observed generally only in one eye.

In the 2 year carcinogenicity study, significant increases were observed in male rats in the incidences of corneal neovascularization at 300 and 900 ppm metribuzin (incidence of 5/33, 3/33, 20/33*, and 16/38* [p< 0.05] for the 4 dose groups). In female rats, the incidence of small eyes was increased at 300 ppm (incidence of 0/42, 0/34, 4/37*, and 2/41 [p < 0.05]). Other abnormalities observed (eye missing, corneal opacity, corneal scar, corneal ulceration, iris constriction, lens opacity, retinal degeneration, cataract, chromodacryorrhea, and iritis) were not significantly different in treated vs control rats.

F. Clinical Signs and Pathology

Examination of rats for any sign of ill health or systemic toxicity was recorded twice daily. Examination for palpable masses was made once a week. The location, size, consistency, time of first observation and subsequent course were noted for each palpable mass.

Blood samples were obtained from the orbital sinus of the first 20 surviving male and female rats used for the 2 year portion of the study at each dose level at 3, 6, 12, 18, and 24 months. Rats were fasted overnight prior to blood collection, and urine was collected on the same animals in the non-fasted state a week prior to blood collection. Although not mentioned in the methods section of the report, a Table was presented (Table HE1-SUM-INT, page 277) which showed results of hematology measurements in the 1-year toxicity group at what seems sacrifice.

Collected blood was mixed with EDTA anticoagulant for hematological examination, and with no anticoagulant for clinical chemistry measurements.

a) Hematology

The following CHECKED hematological parameters were examined:

- _X_ total leucocyte count*
- _X_ erythrocyte count*
- _X_ hemoglobin*
- _X_ hematocrit*
- _X_ platelet count
- _X_ packed cell volume
- _X_ reticulocyte count
- _-_ total plasma protein*
- _X_ leukocyte differential*
- _X_ mean corpuscular HGB
- _X_ mean corpusc. HGB conc.
- _-_ mean corpusc. volume
- _-_ methemoglobin
- _X_ Heinz bodies

*EPA guideline requirement "-" not analyzed

Results of hematological analysis for the one-year toxicity group is summarized below (Table 6). Only those results showing apparent dose- or time-related trends are described.

i) One Year Toxicity Group

Table 6

Hematological Alterations in Male and Female Rats Given Dietary Metribuzin for One Year[a]

	Males				Females			
	0	30	300	900	0	30	300	900
WBC ($10^3/mm^3$)	5.8± 1.3	7.1±* 1.7	6.9± 0.7	6.8±* 0.9	3.2± 0.5	3.7±* 0.3	3.7±* 0.6	3.8±* 0.4
MCV (um^3)	48.5± 1.1	48.4± 0.5	47.8± 0.4	47.7±* 0.9	53.1± 0.4	53.5±* 0.3	54.2± 3.5	51.8±* 1.1
MCHC (g/dl)	35.0± 0.4	34.5±* 0.6	35.1± 0.4	35.5±* 0.3	34.8± 0.5	34.5± 0.3	34.4±* 0.2	35.8±* 0.4
platelets ($10^3/mm^3$)	788± 70	787± 103	825± 44	878±* 60	699± 38	723± 44	735± 63	719± 85

[a]data taken from Table HE1-SUM-INT, pages 277-278 of the report.

A statistically significant increase in white blood cells of 22% and 17% was reported for male rats at the 30 and 900 ppm dose levels. White blood cells were elevated as well at the 300 ppm dose level by 19%, but were apparently not statistically significant. In female rats, statistically significant increases in white blood cells of 16-18% were observed at all dose levels.

Changes in MCV and MCHC were also observed in both male and female rats assigned to the one-year portion of the study, and although noted as statistically significant at the 900 ppm dose in males and the 300 and 900 ppm dose levels in females, the changes were slight (1-2%). Platelet count appeared increased in treated groups of male and female rats, and was noted as statistically significant in male rats at the 900 ppm dose level. However, as with MCV and MCHC, the changes were slight (~ 5%) and no definitive dose-related trend was apparent.

ii) Two-Year Carcinogenicity Group

The hematological alterations observed in rats assigned to the 2-year carcinogenicity portion of the study were similar in nature to those observed in the rats assigned to the one-year toxicity group. That is, minor decreases were sometimes observed in MCV in male and female rats at the 300 and 900 ppm dose levels, as were minor increases in MCHC. Hemoglobin concentration was also decreased slightly in both sexes at later times in the study (12 and 24 months), but in no instance did this exceed 5%, even at the high dose. As with the rats assigned to the one-year study, increases in platelets were observed in male rats primarily at the 900 ppm dose level, and at 6 months, was statistically significant (914 ± 72 vs 859±39 in controls; units: $10^3/mm^3$). However, this represents only a 6% increase, and there was only a slight dose-related trend. In female rats, increases in platelets were similar to that observed in males. Results for the 2-year group were summarized in Table HE1-SUM, pages 280-289 of the report.

b) **Clinical Chemistry:**

Blood samples were obtained for blood chemistry measurements as stated above. The following CHECKED parameters were measured:

_X_ glucose*
_X_ albumin*
_X_ globulin (calculated)
_X_ creatinine
_X_ total bilirubin*
_X_ direct bilirubin
_-_ indirect bilirubin
_X_ urea nitrogen*
_X_ total protein*
_X_ cholesterol*
_X_ triglycerides
_-_ electrophoretic protein fractions

_X_ calcium*
_X_ inorganic phosphate*
_X_ sodium*
_X_ potassium*
_X_ chloride*

_X_ AST(SGPT)*
_X_ ALT(SGOT)*
_X_ alkaline phosphatase
_X_ creatine kinase*
_X_ lactate dehydrogenase
_-_ sorbitol dehydrogenase
_X_ gamma glutamyl trans-peptidase
_-_ ornithine carbamyl transferase
_X_ thyroxine (T4)
_X_ triiodothyronine (T3)

*EPA guideline requirement

"-" not examined

Significant findings in blood chemistry from rats assigned to the toxicity portion of the study are summarized below at the time points measured in this study (Table 7):

Table 7
Clinical Chemistry Alterations in Male and Female Rats Administered Metribuzin in the Diet for One Year[a]

	Males				Females			
	0	30	300	900	0	30	300	900
T4 (mg/dl)	4.89± 0.66	6.49±* 0.5	7.04±* 0.55	5.63±* 1.01	3.59± 0.77	4.70±* 1.06	5.14±* 0.61	3.96± 0.75
T3 (mg/dl)	0.92± 0.24	0.64±* 0.16	0.69±* 0.16	0.66±* 0.21	0.71± 0.14	0.59± 0.75	0.75± 0.13	0.81± 0.17
cholesterol (mg/dl)	89± 15	87± 9	90± 8	121±* 46	108± 13	119± 10	128±* 6	148±* 18

[a]data taken from Table CC3-SUM-INT, pages 340-346 of the report.

The primary effects observed in the one-year treatment group were significant increases in serum T4 levels at the 30 and 300 ppm dose levels, and an apparent dose-related increase in serum cholesterol. The magnitude of increase for T4 was similar for male and female rats at 30 and 300 ppm metribuzin (~ 30%), but the decrease in T3 was higher in males than in females. Statistical significance for the increase in serum cholesterol was achieved at 300 ppm metribuzin in female rats vs 900 ppm metribuzin in male rats.

Results of serum chemistry measurements from rats assigned to the 2-year (carcinogenicity) portion of the study are summarized below (Table 8):

Table 8
Clinical Chemistry Alterations in Male and Female Rats Administered Metribuzin in the Diet for Two Years[a].

91 Days

	Males				Females			
	0	30	300	900	0	30	300	900
T4 (mg/dl)	6.22± 0.67	9.75±*[1] 1.32	7.77±*[1] 1.04	5.74± 0.88	4.38± 0.84	5.60±* 0.72	5.69±* 0.84	3.50±* 0.51
T3 (mg/dl)	1.06± 0.20	0.88±* 0.20	0.95±* 0.22	1.10±* 0.25	1.10± 0.14	0.92*± 0.15	1.08± 0.22	1.09± 0.14
cholesterol (mg/dl)	55± 7	55± 5	65±* 8	72±* 7	84± 6	82± 8	98±* 8	107±* 11

182 Days

T4 (mg/dl)	5.59± 0.46	8.29±* 1.06	7.89±* 0.96	5.98± 0.74	3.70± 0.75	4.69±* 1.09	4.84±* 0.94	3.25± 0.52
T3 (mg/dl)	1.26± 0.23	1.02±* 0.22	0.80±* 0.18	1.05±* 0.32	1.23± 0.17	0.95±* 0.16	1.03±* 0.14	1.10±* 0.12
cholesterol (mg/dl)	54± 5	59±* 7	64±* 7	78±* 9	93± 9	103± 16	111±* 10	111±* 14

Table 8, cont.

364 Days

	Males				Females			
	0	30	300	900	0	30	300	900
T4 (mg/dl)	5.68± 0.69	8.02±*1 0.74	8.13±*1 0.95	7.24±* 1.04	2.55± 0.68	4.93±* 0.89	4.70±* 0.97	3.76±* 0.80
T3 (mg/dl)	1.01± 0.16	0.86±* 0.14	0.77±* 0.19	0.88± 0.24	0.71± 0.14	0.93±* 0.16	0.83± 0.15	0.96±* 0.18
cholesterol (mg/dl)	91± 12	78±* 7	99± 13	108±* 14	123± 15	119± 13	139±* 18	157±* 15

546 Days

T4 (mg/dl)	4.90± 0.74	5.95±*1 1.23	6.70±* 0.91	6.32±* 1.08	3.40± 0.64	4.14±* 1.11	4.49±* 0.51	3.22± 0.61
T3 (mg/dl)	0.74± 0.14	0.75± 0.16	0.62±* 0.10	0.65± 0.15	0.94± 0.15	0.70±* 0.20	0.82±* 0.15	0.85± 0.13
cholesterol (mg/dl)	118± 27	123± 42	123± 21	122± 28	106± 15	105± 17	121±* 21	153±* 44

Table 8, cont.

728 Days

	Males				Females			
	0	30	300	900	0	30	300	900
T4	2.67±	3.29±	3.46±	2.94±	2.47±	3.50±*	3.88±*	3.35±*
(mg/dl)	1.26	1.12	1.00	1.04	0.45	0.78	0.84	0.94
T3	0.67±	0.68±	0.52±*	0.49±*	0.81±	0.75±	0.68±*	0.81±
(mg/dl)	0.14	0.18	0.15	0.18	0.14	0.16	0.08	0.17
cholesterol	156±	148±	135±	135±	139±	129±	165±	165±
(mg/dl)	43	73	39	53	15	13f	18	15

[a]data taken from Table CC3-SUM, pages 348-376 of the report.

[1]indicates value is outside historical control range from data provided by the registrant (pages 4341-4352 of the report). No historical data were provided for T3 levels.

The major alterations observed in serum chemistry in the present study were, as shown, increased serum levels of thyroxine (T4), decreased levels of triiodothyronine (T3), and increased levels of cholesterol. There was no clear dose-response for the elevation in T4 or the decrease in T3, but as noted, values for male rats sometimes fell outside historical control range.

The registrant made the argument that although changes in T4 and T3 levels were observed, these should not be considered toxicologically relevant, as there were no significant toxicologic effects on the test animals as a result of these changes. Whether or not a potentially significant effect does occur cannot be determined from these data, as levels of TSH were not measured in this study. TSH levels would at least give some indication of the mechanism of the effect, as only unproven hypotheses can be generated otherwise with regard to how metribuzin exerts this particular effect.

Statistically significant elevations in serum cholesterol were also observed in male and female rats in this study at the 300 and 900 ppm dose levels. These increases appeared dose-related in both sexes. The relationship of this change to the changes in serum T4 and T3, if any, is not known from these data.

c) Urinalysis:

Overnight urine samples were collected from the same rats as used for determination of serum chemistry and hematology.

The following CHECKED parameters were examined:

_X_ appearance*	_X_ glucose*
_X_ volume*	_X_ pH
_X_ specific gravity*	_X_ bilirubin*
_X_ protein*	_X_ urobilinogen
_X_ ketone*	_-_ nitrate
_X_ blood*	___
_X_ sediment analysis*	___

*EPA guideline requirement "-" not examined

Note: Urinalysis results were summarized in Table UR1-SUM and UR2-SUM, pages 379-418 of the report.

No toxicologically significant alterations in measured urine parameters were evident in this study.

G. **Macroscopic Observations** (Tables GP2-SUM-INT and GP2-SUM)

All rats sacrificed in extremis or at study termination were killed by carbon dioxide asphyxiation and subjected to gross necropsy. The necropsy was a systematic gross examination of each animal's general physical condition, body orifices, external and internal organs, and tissues. A report of macroscopic observations in this study was made on pages 4549-4555, and summary tables were shown on pages 420-451 for the 1-year sacrifice group, and on pages 453-525 for the 2-year sacrifice group.

Examination of the data from rats sacrificed at one year showed no apparent treatment-related macroscopic abnormalities. Data for rats assigned to the carcinogenicity (2-year) portion of this study showed several macroscopic abnormalities, which are summarized in the following table (Table 9):

TABLE 9
Incidence of Macroscopic Lesions in Male and Female Rats Given Dietary Metribuzin for Two Years[a]

	Males				Females			
Dose (ppm)	0	30	300	900	0	30	300	900
No. examined	50	50	50	50	50	50	50	50
Liver								
discolored zone	5(10)*	3(6)	8(16)	13(26)				
Adrenals								
enlarged	2(4)	2(4)	3(6)	5(10)				
mass	0(0)	0(0)	0(0)	1(2)				
Thyroid								
enlarged	3(6)	2(4)	7(14)	8(16)	0(0)	1(2)	1(2)	3(6)
Eyes								
opacity	6(12)	10(20)	15(30)	12(24)				
exophthalmos	0(0)	1(2)	1(2)	2(4)				
Abdomen								
No. examined	39	43	42	40				
enlarged	1(2.6)	3(7.0)	3(7.1)	6(15)				
Epididymis								
mass	2(4)	2(4)	2(4)	4(8)				

Table 9, cont.

	Males				Females			
Dose (ppm)	0	30	300	900	0	30	300	900
No. examined	50	50	50	50	50	50	50	50
Ovaries								
cyst					4(8)	3(6)	5(10)	7(14)

* incidence (%)

As noted above, macroscopic changes in male rats were evident primarily at the 300 and 900 ppm dose levels , and included discolored zone in the liver, enlarged adrenal and thyroid gland, ocular opacity, enlarged abdomen, and epididymal mass. The only macroscopic lesions of note in female rats were ovarian cyst, increased in incidence at the 300 and 900 ppm dose levels, and enlarged thyroid, increased in incidence at 300 and 900 ppm metribuzin. The registrant stated (page 4553) that none of these changes were statistically significant.

H. **Organ Weights** (Tables OW1K-SUM -INT and OW1K-SUM, pages 526-542 of report).

Organs to be weighed were obtained from all animals dying or killed during the study. The following organs were weighed: adrenals, brain, heart, kidneys, liver, lungs, spleen, testes, and ovaries. Group mean and individual organ weights were provided. Organ/body weight ratios were also provided.

In the treatment group assigned to receive test article for one year, the weight of the liver, kidney, brain, thyroid (males only), and testes were affected. These changes are summarized below (Table 10):

Table 10
Organ:Body Weight Ratios in Male and Female Rats
Administered Metribuzin in the Diet for One Year[a]

	Males				Females			
	0	30	300	900	0	30	300	900
term. b.w.	409.1± 22.2	410.5± 25.9	414.8± 15.6	400.2± 22.4	224.4± 35.3	225.1± 9.2	211.2± 8.4	205.2± 10.9[a]
brain	1.96±0.04	1.97±0.05	2.01±0.05	1.92±0.14	1.80±0.05	1.80±0.04	1.83±0.03	1.78±0.04
brain/ b.w.	0.48±0.02	0.48±0.02	0.48±0.02	0.48±0.04	0.81±0.09	0.80±0.02	0.87±0.03[a]	0.87±0.05[a]
thyroid	0.028± 0.00	0.035± 0.04	0.034± 0.00[a]	0.037± 0.01[a]	0.024± 0.01	0.02± 0.005	0.022± 0.004	0.023± 0.008
thyroid / b.w.	0.0067± 0.0011	0.0085± 0.0033[a]	0.0082± 0.0008[a]	0.0093± 0.0017[a]	0.0106± 0.0050	0.0088± 0.0023	0.0105± 0.0020	0.0109± 0.0035
kidneys	3.4±0.22	3.3±0.17	3.51±0.18	3.46±0.28	1.93±0.14	1.93±0.10	1.91±0.11	1.91±0.09
kidney / b.w.	0.82±0.03	0.81±0.04	0.84±0.02	0.86±0.05[a]	0.87±0.08	0.86±0.03	0.90 ±0.05	0.93±0.03[a]
liver	14.94±1.5	15.66±0.97	16.19±1.1[a]	16.80±1.3[a]	8.35±0.87	8.46±0.47	8.50±0.3	8.74±0.67
liver / b.w.	3.64±0.25	3.82±0.23	3.90±0.20[a]	4.19±0.21[a]	3.76±0.36	3.76±0.23	4.03±0.16[a]	4.26±0.2[a]
testes	3.47±0.84	3.2±0.13	3.4±0.08	3.2±0.26				
testes / b.w.	0.85±0.21	0.78±0.04	0.81±0.03	0.79±0.07				

[a] $p < 0.05$ vs control

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In the one year toxicity group, several changes in organ weights were observed. These included increased absolute brain weight in high dose females (7% over control, $p < 0.05$), increased brain / body weight ratio in 300 ppm and 900 ppm females, increased thyroid weight in males at the 300 and 900 ppm dose levels (21% and 32% increases, respectively; $p < 0.05$), increased thyroid / body weight ratio in males at the 30, 300 and 900 ppm dose levels (27%, 22% and 39% increases, respectively), and increased kidney / body weight ratio in high dose male and female rats.

A summary of changes in absolute and relative organ weights from rats in the 2 year study group are summarized below (Table 11):

Table 11
Organ:Body Weight Ratios in Male and Female Rats
Administered Metribuzin in the Diet for Two Years[a]

	Males				Females			
	0	30	300	900	0	30	300	900
term. b.w.	355.9± 27.7	350.3± 32.5	340.0± 35.1	320.8± 37.1[a]	268.3± 20.9	261.1± 18.1	253.4± 20.7[a]	238.8± 16.6[a]
brain	2.02±0.06	2.01±0.05	2.01±0.06	1.98±0.06	1.83±0.07	1.82±0.05	1.83±0.06	1.81±0.04
brain/ b.w.	0.57±0.04	0.58±0.05	0.60±0.07	0.63±0.08[a]	0.69±0.06	0.70±0.05	0.73±0.06[a]	0.76±0.05[a]
heart	1.21±0.09	1.22±0.12	1.22±0.14	1.18±0.11	0.93±0.09	0.91±0.07	0.88±0.07	0.88±0.04[a]
heart / b.w.	0.34±0.03	0.35±0.04	0.36±0.05	0.37±0.04[a]	0.34±0.04	0.35±0.04	0.35±0.3	0.37±0.03[a]
thyroid	0.029± 0.007	0.031± 0.012	0.033± 0.009	0.036± 0.009[a]	0.022± 0.005	0.021± 0.006	0.026± 0.006[a]	0.025± 0.005[a]
thyroid / b.w.	0.0082± 0.0022	0.0088± 0.0035	0.0099± 0.0025[a]	0.0111± 0.0026[a]	0.0081± 0.0019	0.0082± 0.0021	0.0102± 0.0022[a]	0.0104± 0.0019[a]

Table 11, cont.

	Males				Females			
	0	30	300	900	0	30	300	900
kidney / b.w.	1.03±0.11	1.05±0.16	1.07±0.17	1.16±0.13[a]	0.91±0.05	0.90±0.07	0.95 ±0.08	1.03±0.08[a]
liver	16.63±1.9	16.57±3.1	16.00±2.9	16.73±3.0	11.22±1.7	10.46±1.1	10.95±1.3	11.48±1.5
liver / b.w.	4.70±0.63	4.74±0.86	4.72±0.76	5.22±0.88[a]	4.19±0.6	4.01±0.4	4.33±0.52	4.81±0.58[a]
testes	6.77±2.3	6.21±2.36	6.51±5.6	6.19±2.19				
lung					1.42±0.44	1.28±0.11[a]	1.23±0.09[a]	1.28±0.13[a]
lung / b.w.					0.53±0.19	0.49±0.05	0.49±0.04	0.54±0.06[a]

[a] $p < 0.05$ vs control

As in the one year toxicity group, several changes in absolute organ weight and organ / body weight ratios were observed. These included the following, all of which were statistically significant at the 0.05 level of probability:

a) increased brain / body weight ratio in high dose males (10% vs control) and mid and high dose females (5% and 10% vs control).
b) decreased heart weight in high dose females (15% vs control).
c) increased heart / body weight ratio in high dose males (9% vs control) and high dose females (9% vs control).
d) increased kidney / body weight ratio in high dose males (12% vs control) and females (13% vs control).
e) increased liver / body weight ratio in high dose males (11% vs control) and females (15% vs control).
f) increased thyroid weight in high dose males (24% vs control) and in mid and high dose females (18% and 13% vs control, respectively).

g) increased thyroid / body weight ratio in mid and high dose males (20% and 35% vs control, respectively) and mid and high dose females (25% and 28% vs control, respectively).

gh) decreased lung weight in low, mid, and high dose females (10%, 13%, and 10%, respectively vs control)

I. **Microscopic Observations (Note:** Evaluation of tissues was performed by Colorado Pathology Services, Inc.)

Samples of the following tissues were preserved in 10% buffered formalin for possible microscopic examination.

Digestive

_x_ tongue
_x_ salivary glands*
_x_ esophagus*
_x_ stomach*
_x_ duodenum*
_x_ jejunum*
_x_ ileum*
_x_ cecum*
_x_ colon*
_x_ rectum*
_x_ liver*
_x_ pancreas*
_x_ gall bladder*

Respiratory

_x_ trachea
_x_ lungs*
_x_ nasal cavity

Cardiovascular

_x_ aorta*
_x_ heart*
_x_ bone marrow
_x_ lymph nodes*
_x_ spleen*
_x_ thymus*

Urogenital

_x_ kidneys*
_x_ urinary bladder*
_x_ testes*
_x_ epididymides*
_x_ seminal vesicle*
_x_ prostate
_x_ ovaries
_x_ uterus*
_x_ vagina
_x_ cervix
_x_ clitoral gland

Neurologic

_x_ brain*
_x_ peripheral nerve*
_x_ spinal cord (3 levels)*
_x_ pituitary*
_x_ eyes

Glandular

_x_ adrenals*
_x_ lacrimal gland
_x_ mammary gland
_x_ parathyroids*
_x_ thyroids*
_x_ preputial gland
_x_ harderian gland

Other

_x_ bone (femur)
_x_ skeletal
_x_ muscle
_x_ skin*
_x_ all gross lesions*

*EPA guideline requirement "-" not examined

Tissues were prepared for microscopic examination by embedding in paraffin wax, cutting thin sections (5µm), and staining with hematoxylin and eosin. Microscopic examination was performed on the above tissues from all rats in control and high dose groups sacrificed at 52 weeks, on all rats killed at 104 weeks, and on all decedent rats.

1a) Neoplastic and Non-Neoplastic Observations-One Year

The following observations were noted in rats assigned to the one year toxicity group (Table 12):

TABLE 12

Incidence of Neoplastic and Non-Neoplastic Lesions in Male and Female Rats Given Dietary Metribuzin for One Year[a]

	Males				Females			
Dose (ppm)	0	30	300	900	0	30	300	900
Head								
No. of Animals Examined	20	10	10	20	20	10	10	20
Kidney- mild nephropathy	9	2	7	16	0	0	0	0
Pituitary- mild hyperplasia	1	0	0	4	3	0	0	2
Testes- interstitial cell hyperplasia	5	3	7	10				
Thyroid follicular cell hyperplasia	0	0	4	11	0	0	0	0

[a]data from Table 1, pages 543-552 of the report.

With the exception of follicular cell hyperplasia, the listed microscopic findings above were considered as naturally occurring. However, in the case of kidney nephropathy and interstitial cell hyperplasia of the testes, there appeared to be dose-related effect at 900 ppm in male rats. With regard to the follicular cell hyperplasia of the thyroid, the report stated (page 4566) that "the lesion was characterized on low magnification by a slight increase in the size of the thyroid gland. On

higher magnification, this enlargement was due to an increased diameter of the centrally located thyroid gland follicles and an increase in follicular epithelial cell height. This non-neoplastic finding...was considered to be related to the dietary administration of SENCOR."

Neoplastic observations in the one year toxicity group were spontaneous and unrelated to treatment with test chemical.

1b) Neoplastic and Non-Neoplastic Observations-104 Weeks (pages 553-574 of the report)

Summary of microscopic observations which appeared to be increased at the higher doses of metribuzin is made below (Table 13):

TABLE 13

Incidence of Non-Neoplastic and Neoplastic Lesions in Male and Female Rats Given Dietary Metribuzin for 104 Weeks [a]

	Males				Females			
Dose (ppm)	0	30	300	900	0	30	300	900
No. Animals Examined	50	50	50	50	50	50	50	50
Eye								
R. optic nerve atrophy	2	1	1	2	1	4	8	6
Harderian Gland								
chronic inflammation	3	1	4	7	5	1	0	2
Liver								
telangiectasis	15	8	13	20	3	2	5	8
Pancreas								
atrophy	7	6	6	9	1	1	4	5
islet cell adenoma	2	4	5	5	2	1	1	1

Table 11, cont.

	Males				Females			
Dose (ppm)	0	30	300	900	0	30	300	900
Pituitary								
cyst	0	4	2	3	9	9	15	13
hyperplasia	5	7	8	8	3	6	5	2
Spleen								
brown pigment	4	5	6	6	11	3	12	12
Thyroid								
follicular adenoma	0	0	2	2	0	1	1	0
follicular hyperplasia	0	0	0	38	0	0	0	0
parafollicular cell adenoma	9	10	6	8	3	6	7	6
Urinary bladder								
malignant mesothelioma	0	1	0	3	0	0	0	0
Testis								
tubular degeneration	1	3	2	5				

Listed above are the non-neoplastic and neoplastic observations which appeared to be increased at either the 300 ppm and 900 ppm dose levels, or both. The most obvious change observed was an increase in thyroid follicular hyperplasia in male rats at the 900 ppm dose level. Although thyroid weight was increased in both male and female rats, it was only in males that this lesion appeared in increased incidence. The registrant acknowledged this lesion to be dose-related and also related to administration of metribuzin. While it appeared that some tumor types were increased at 300 and 900 ppm metribuzin (such as pancreatic islet cell adenoma in males, follicular adenoma in males, parafollicular cell adenoma in females, and malignant mesothelioma in males), the registrant stated on page 4571 of the report that "statistical analysis, including time-to-tumor (Peto) analysis, Chi-Square and Fisher's exact tests did not reveal any significant increases in the occurrence of neoplasms."

The microscopic evaluation of tissues in this study, in addition to being examined by an outside source, were also subjected to an in-house peer review to corroborate the evidence found by the outside contractor. In sum, the in-house peer review agreed with the conclusions drawn by the outside contractor regarding the pathological observations made in this study. The thyroid was officially stated as a target organ for metribuzin, and the peer review committee made a diagnosis of minimal, bilateral, diffuse, follicular hyperplasia thought to be related to administration of test substance. The incidence summary of this lesion is made below (from page 4591 of the report):

MALES:	CONTROL	30 PPM	300 PPM	900 PPM
1-YEAR INTERIM GROUP:	0/20 (0%)	0/10 (0%)	4/10*[t] (40%)	11/20* (55%)
2-YEAR ONCOGENICITY GROUP:	0/50 (0%)	--[u] (--)	0/50 (0%)	38/50* (76%)
FEMALES:				
1-YEAR INTERIM GROUP:	0/20	--	--	0/20 (0%)
2-YEAR ONCOGENICITY GROUP:	0/50 (0%)	--	--	0/50 (0%)

[t]"*" means statistically significant at the $p \leq 0.05$ level.

[u]"--" means not evaluated due to an established NOEL at a higher dose level.

III. DISCUSSION

In the present study, the chronic toxicity and carcinogenicity of metribuzin were assessed in male and female Fischer 344 rats. Rats received technical metribuzin in the diet for either one year (toxicity group) or two years (carcinogenicity group) at dose levels of 0, 30, 300, and 900 ppm (0, 1.3, 13.8, and 42.2 mg/kg/day for males; 0, 1.6, 17.7, and 53.6 mg/.kg/day for females) .

Mortality (survival) was not significantly altered in test article treated rats of either sex in comparison to control rats. Absolute body weight was slightly but significantly decreased in male rats at the 900 ppm dose level, and in female rats at the 300 and 900 ppm dose levels. These decreases were observed at week 13 of the study for female rats, and continued until study termination. Significant decreases in body weight gain of greater than 10% were observed for male rats at the 900 ppm dose level, and for female rats at the 300 and 900 ppm dose levels. Decreases in body weight gain exceeded the decreases in food consumption at the 300 and 900 ppm dose levels, supporting a conclusion of test article related toxicity.

No ophthalmologic effects from administration of test article were evident in male and female rats assigned to the one year toxicity group. In rats assigned to the two year portion of the study,

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however, an increase in corneal neovascularization was observed in male rats at the 300 and 900 ppm dose levels, while the incidence of small eyes in female rats was increased significantly at 300 ppm. The incidence of small eyes did not increase in female rats at 900 ppm.

The hematological parameters significantly affected in this study were white blood cell count, mean cell volume, mean corpuscular hemoglobin concentration, and platelet count. While significant changes were observed at the 300 and 900 ppm dose levels, these changes were small in comparison to controls (1-5%), and so were not considered indicative of treatment with metribuzin.

The most biologically relevant change in serum chemistry involved increases in levels of thyroxine (T4) and decreases in levels of triiodothyronine (T3). In general, an increase in T4 levels and a decrease in T3 levels could be observed at 30 and 300 ppm for male and female rats, but this trend did not continue at the 900 ppm dose. In addition, it was difficult to identify a potential mode of action for metribuzin in this respect, as TSH levels were not measured. Although the changes in T4 and T3 occurred at the lowest dose level (30 ppm), these were not considered biologically relevant by the registrant, as other systemic effects were not observed at this dose. This conclusion seems appropriate in light of the available data.

Analysis of urine from rats assigned to the one year portion of the study showed no significant treatment related effects.

Observations at gross necropsy included increased size of the thyroid in male and female rats at the 300 and 900 ppm dose levels, an increase in the incidence of female rats with ovarian cysts at 900 ppm (from 4 to 7 rats), exophthalmos in 2 high dose male rats vs 0 in controls, enlarged adrenals in 5 high dose males vs 2 controls, discolored zone in the liver of 13 high dose males vs 5 controls, and epididymal mass in 4 high dose males vs 2 control. There did not appear to be any microscopic support for the macroscopic changes recorded, except for thyroid.

Several organ weight changes, both absolute and relative, were observed in male and female rats at 300 and 900 ppm metribuzin. Rather than reiterate all the changes observed, the reader is referred to Tables 9 and 10 of this review. It is noted that the greatest change observed was an increase in thyroid weight at 300 and 900 ppm in male rats assigned to the one year portion of the study, and increased thyroid weight at 300 and 900 ppm in male and female rats assigned to the two year portion of the study. The changes seen in thyroid weight were dose-related and related to administration of test article. This macroscopic change was supported by microscopic evidence of follicular cell hyperplasia in male rats at the 300 and 900 ppm dose levels. Such evidence was not reported for female rats at these dose levels.

A number of microscopic alterations were reported in Table 11 of this review. The neoplastic changes reported at 300 and 900 ppm (pancreatic islet cell adenoma in males, follicular adenoma in thyroid of males, parafollicular adenoma in males, malignant mesothelioma in males) were stated by the registrant as not statistically significant, based on statistical analysis of the tumor data. It is noted that thyroid effects were significant at the microscopic level for male rats at the 900 ppm dose level, but not for female rats.

The highest dose of test article examined in this study was 900 ppm in both male and female rats. This dose caused a body weight gain decrement of greater than 10% during the first 13 weeks of treatment in both sexes of rats. This weight gain decrement persisted throughout the study in both sexes. In addition, ophthalmoscopic abnormalities in male rats, increased absolute and relative organ weights (particularly with regard to the thyroid gland), and increases in non-neoplastic pathology were identified at the 900 ppm dose level. In light of these systemic effects, the 900 ppm

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dose level is considered a maximum tolerated dose (MTD) for the test article in this study.

IV. CONCLUSIONS

Technical metribuzin was administered to male and female rats in the diet for either 52 or 104 weeks at doses of 0, 30, 300, and 900 ppm (0, 1.3, 13.8, and 42.2 mg/kg/day in males; 0, 1.6, 17.7, and 53.6 mg/kg/day in females). In males and females, systemic toxicity in the form of reduced body weight gain, ophthalmologic abnormalities, changes in absolute and relative organ weights, and increases in the incidence of non-neoplastic pathology were evident at the 900 ppm dose level, establishing this as a maximum tolerated dose for the study. Statistically significant increases in blood levels of thyroxine (T4) and statistically significant decreases in blood levels of triiodothyronine (T3) were observed at all dose levels in male and female rats dosed for either one or two years with technical metribuzin beginning at 91 days, and continuing until study termination in the 2 year group. Thyroid / body weight ratio was significantly increased at all dose levels of metribuzin in male rats assigned to the one year portion of the study. There was no definitive evidence of a tumorigenic response to metribuzin in this study.

The data in this study support the conclusion of no evidence of carcinogenicity for technical metribuzin.

The No Observed Effect Level (NOEL) < 30 ppm

The Lowest Observed Effect Level (LEL) = 30 ppm (males and females; increased absolute and relative weight of the thyroid; decreased lung weight; significant changes in T4 and T3 levels).

The Maximum Tolerated Dose (MTD) = 900 ppm (males and females; decreased body weight and body weight gain).

V. CLASSIFICATION

chronic toxicity - supplementary
carcinogenicity - minimum

This study satisfies the guideline requirements (§83-5) for a carcinogenicity study in rats, but does not satisfy the guideline requirements for a chronic toxicity study in rats, due to the lack of establishment of a systemic NOEL.